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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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TOWNSEND AND TOWNSEND AND CREW LLP
TWO EMBARCADERO CENTER
8TH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
MILLER, MARINA I	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 05/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/510,378	CRONIN ET AL.	
	Examiner	Art Unit	
	Marina Miller	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *82-133* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *82-89 and 93* is/are allowed.

6)☒ Claim(s) *90-92 and 94-133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' submission filed on 10/03/2005 is acknowledged. Claims 82-133 are pending. Claims 1-81 are cancelled. Claims 82-133 presently are under examination.

Applicants' arguments have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are applied.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New claims 95-133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Claims 95, 102, 111, and 122 recite the limitation "first probe comprises a first sequence that is complementary to an exon or an intron of a gene." In response filed 10/03/2005, applicants pointed to page 14, lines 10-20, and page 16, lines 33-36 for support for the new limitation. The specification discloses on page 14: "[t]he invention provides a number of strategies for comparing a polynucleotide of known sequence (a reference sequence) with variants of that sequence (target sequences). The comparison can be performed at the level of

entire genomes, chromosomes, genes, exons or introns, or can focus on individual mutant sites and immediately adjacent bases." (p. 14, lines 10-15). The specification discloses on page 16: "[t]he length of a reference sequence can vary widely from a full-length genome, to an individual chromosome, episome, gene, component of a gene, such as an exon, intron or regulatory sequence." (p. 16, lines 33-35). Thus, the specification generally discloses reference and target sequences, but does not specifically disclose a *first probe* comprising a *first sequence complementary to an exon or an intron* of a gene.

Claims 95, 102, 111, and 122 further recite "first probe comprises a first sequence ... wherein said sequence corresponds to at least one region of variation corresponding to a splice sequence." Applicants pointed to page 63, lines 23-37 for support. The specification discloses on page 63: "[a]bout 90% of all mutations having phenotypic effects occur in coding regions. Other mutations occur in splice site consensus sequences, introns and the promoter region. The most common cystic fibrosis mutation is three-base deletion resulting in omission of amino acid." (p. 63, lines 23-27). Thus, the specification generally discloses that mutations may occur in splice sites and intron regions, but it does not disclose a first probe comprising a sequence which corresponds to a region of variation corresponding to a splice sequence.

Claims 95, 102, 111, and 122 further recite "second probe comprises a second sequence that is complementary to an exon-intron boundary of said gene." Applicants pointed to page 63, lines 15-17 and page 70, line 31 to page 71, line 11 for support. The specification discloses on page 63: "[the CFTR gene ... has 27 exons. ... Wild type genomic sequence is available for all exonic regions and exon/intron boundaries [for CFTR gene]." (p. 63, lines 15-17). The specification discloses on page 70: "[o]ne illustrative chip bears 1296 probes covering the full

length of exon 10 of the CFTR gene arranged in ... array. ... The probes in the array can have any length ... and can be used to detect and sequence any single-base substitution and any deletion within the 191-base exon." (p. 70, lines 31-37). Thus, the specification discloses that CFTR genomic sequences of exons and exon/intron boundary regions are known, and probes spanning exon 10 of the CFTR gene. However, the specification does not disclose a *second probe* comprising a second sequence *that is complementary to an exon-intron boundary of a gene*.

Claims 95, 102, and 111 also recite "probes of between 3 and 100 nucleotides in length." Applicants pointed to page 20, lines 33-36 for support. The specification discloses on page 20: "the probes in the first set have interrogation positions correlating to at least 3, 10, 50, 100 ... contiguous nucleotides." (p. 20, lines 33-35). Thus, the specification only discloses *specific* lengths (*i.e.*, at least 3, 10, 50, 100, *etc.* bases), but it does not disclose a *range* beginning at 3 and ending at 100 nucleotides. The specification only discloses ranges of 6-30 and 9-21 nucleotides on pages 20 and 23.

Claim 122 recites the limitation "oligonucleotides of between 5 and 100 nucleotides in length." Applicants provided a general list of citations from the specification related to claims 111-133, but did not specifically point to pages from the specification supporting the instant limitation. The examiner reviewed the listed citations, but did not find support for the limitation, Specifically, the specification only discloses *specific* lengths (*i.e.*, at least 3, 10, 50, 100, *etc.* bases), but it does not disclose a *range* beginning at 5 and ending at 100 nucleotides. The specification only discloses ranges of 6-30 and 9-21 nucleotides on pages 20 and 23.

Claims 95 and 102 recite the limitation "detecting ... variation in the splicing of a gene." Claims 111 and 122 recite the limitation identifying "differentially spliced gene product." Applicants pointed to page 63, lines 23-37 for support. The specification discloses on page 63: "[a]bout 90% of all mutations having phenotypic effects occur in coding regions. Other mutations occur in splice site consensus sequences, introns and the promoter region. The most common cystic fibrosis mutation is three-base deletion resulting in omission of amino acid." (p. 63, lines 23-27). Thus, the specification discloses identifying mutations which are "variations" in the gene itself, but it does not support detection of differential gene splicing. Specifically, a "mutation" does not necessarily mean that the gene is spliced differently; it only means that the sequence itself is different. Thus, if the mutation is not in a splice junction, it would not cause "variation" in splicing.

Claims 96 and 104 recite the limitation "wherein said probe sequences are publicly available." Applicants pointed to page 63, lines 15-21 for support. The specification discloses on page 63: [w]ild type genomic sequence is available for all exonic regions and exon/intron boundaries [for CFTR gene]." (p. 63, lines 15-17). The specification discloses only that the CFTR wild type genomic *sequence* is available (*i.e.*, known), but it does not disclose that *any* probe sequences and/or *actual* oligonucleotides are "publicly available." Probe sequences may be based on genomic sequences, but probes must be specifically designed, and therefore are not "publicly available" simply because a genomic sequence is available.

Claim 124 recites steps of hybridizing a plurality of different RNA or cDNA with partially unknown composition derived from a sample with different cDNA molecules with partially unknown composition derived from a second sample, and identifying molecules with

the unpaired region. Applicants provided a general list of citations from the specification related to claims 111-133, but did not specifically point to pages from the specification supporting the instant limitation. The examiner reviewed the listed citations, but did not find support for the limitations recited in claim 124.

Thus, claims 95-133 are rejected for reciting new matter.

Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 90-92 and 94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 90 was rejected as being indefinite because the limitation "the segment" recited in line 8 did not have antecedent basis. Applicants amended claim 90 to recite "the probe" in line 8. However, it is not clear which "probe" is intended because claim 90 recites, for example, in previous lines, "an array of oligonucleotide probes", "first and second sets of oligonucleotide probes", and a "plurality of probes". Nowhere does the claim previously recite a single probe which is clearly the antecedent basis for "the probe" of line 8. Thus, it is unclear which, if any, of the previously recited multiple probes is intended to be the antecedent basis for "the probe" of line 8. As the intended limitation is not clear, claims 90-92 and 94 are indefinite. This rejection may be overcome by amending line 8 to recite "wherein the complementary probe includes ...," if this limitation is consistent with applicant's intent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 95-100, 102-106, 108-117, 119-123, 125-128, and 130-133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fodor, US Patent 5,445,934, in view of Romano, US Patent 5,660,979, and further in view of Buchwald, US Patent 5,681,942.

Fodor discloses a method and a device for forming an array of polymers (abstract). Fodor discloses providing nucleic acid probes and arranging and immobilizing a plurality of sets of probes on a solid support (claims 1-10 and fig. 1-7).

Fodor does not disclose a first probe complementary to an exon or intron and a second probe complementary to an exon-intron boundary and detecting variation in the splicing of a gene.

Romano discloses hybridizing a first probe with an exon and a second probe with exon-exon junction for detecting splice variants (claim 1).

Romano does not specifically disclose a second probe complementary to an exon/intron boundary.

Buchwald discloses hybridizing different probes with different regions of a gene (*e.g.*, exon, intron, or sequence spanning an intron-exon boundary) (col. 29, lines 19-29). Buchwald discloses primers designed based on a sequence of FA gene (col. 6, lines 47 to col. 7, line5).

Buchwald discloses probes 15-20 nucleotide in length (col. 29, lines27-29). Buchwald discloses mutations responsible for Fanconi Anemia human disorder.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method and the device of Fodor to make an array/device comprising primers complementary to exons and exon-intron regions, such as taught by Romano and Buchwald, where the motivation would have been to permit the analysis of these regions for potential splice site mutations, as taught by Buchwald, col. 7-8, bridging paragraph.

Claims 95-123 and 125-133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fodor, US Patent 5,445,934, in view of Kawasaki, US Patent 5,057,419, and further in view of Buchwald, US Patent 5,681,942.

Fodor discloses a method and device for forming an array of polymers (abstract), as set forth above.

Fodor does not disclose a first probe complementary to an exon or intron and a second probe complementary to exon-intron boundary and detecting variation in the splicing of a gene.

Kawazaki discloses hybridizing a first probe with an exon and a second probe with exon-exon junction for detecting splice variants (claim 8). Kawazaki discloses primers for detecting acute and chronic leukemia (col. 4, lines 64-68).

Kawazaki does not specifically disclose a second probe complementary to an exon/intron boundary.

Buchwald discloses hybridizing different probes with different regions of a gene (*e.g.*, exon, intron, or sequence spanning an intron-exon boundary) (col. 29, lines 19-29). Buchwald

discloses primers designed based on a sequence of FA gene (col. 6, lines 47 to col. 7, line5). Buchwald discloses probes 15-20 nucleotide in length (col. 29, lines27-29). Buchwald discloses mutations responsible for Fanconi Anemia human disorder.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method and the device of Fodor make an array/device comprising primers complementary to exons and exon-intron regions, such as taught by Kawazaki and Buchwald, where the motivation would have been to permit the analysis of these regions for potential splice site mutations, as taught by Buchwald, col. 7-8, bridging paragraph.

Conclusion

Claims 82-89 and 93 are allowed. Claims 90-92 and 94-133 are rejected.

The following is an examiner's statement of reasons for allowance:

Applicants convincingly argue in the response filed 10/30/2003 that the prior art of Mundy, U.S. Patent, 4,656,127, does not disclose analysis of multiple interrogation positions. Also, Mundy teaches only two different probes wherein claim 88 requires at least seven probes, at least four of which are different from one another.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marina Miller whose telephone number is (571)272-6101. The examiner can normally be reached on 8-5, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, Ph. D. can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marina Miller
Examiner
Art Unit 1631

MM

MARJORIE A. MORAN
PRIMARY EXAMINER
5/10/06